

Reiter's Syndrome

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Case

A thirty-four year old White male was referred for bilateral uveitis. The patient's past medical history was significant for urethritis secondary to chlamydia trachomatis infection that was followed by painless genital sores and joint pain in the right ankle and both knees. He was a carrier of the HLA-B27 gene. The patient's past ocular history was significant for recurrent episodes of bilateral uveitis over the past ten years treated with topical and periocular corticosteroids. The patient underwent laser peripheral iridectomy in the left eye for acute angle closure glaucoma two years earlier.

At the time of the initial exam by us the patient was treated with prednisolone acetate 1% drops in both eyes. He was complaining of blurry vision in the left eye. The visual acuities were 20/25 and 20/200 right and left eye, respectively. The slit lamp exam disclosed 1+ cells in the anterior chamber and vitreous of both eyes. Ophthalmoscopy and fluorescein angiography revealed cystoid macular edema in the left eye.

Because of the recurrent episodes of uveitis that required chronic use of topical corticosteroids over the past ten years, immunosuppressive therapy using methotrexate at the dose of 7.5 mg once a week was begun. Topical ocufen four times a day was initiated in an effort to treat cystoid macular edema in the left eye. The patient was followed every six weeks for monitoring the systemic therapy with methotrexate and activity of uveitis. Topical corticosteroids were discontinued four weeks after the initiation of immunosuppressive therapy. The visual acuities returned to 20/20 in both eyes four months later. A recurrent episode of uveitis in the left eye was noted 8 months later. Therefore, the dose of methotrexate was increased to 12.5 mg/week and the recurrence was treated with periocular and topical corticosteroids. The steroid drops were tapered and discontinued within six weeks later. The visual acuities remained 20/20 in both eyes. On a follow-up visit two months after the recurrent episode of uveitis the patient was complaining of joint pain in the right ankle and both knees. Therefore, Celebrex 200 mg twice daily was prescribed. Five months later a recurrent episode of uveitis in the left eye complicated by angle closure glaucoma was documented. The visual acuity in the left eye dropped to counting fingers.

Therefore, the dose of methotrexate was boosted to 25 mg/week and surgical iridectomy was performed. Two months after the surgery the uveitis was well controlled with systemic methotrexate, and the patient was on no corticosteroids. The visual acuities are 20/20 in both eyes and intraocular pressures are normal.

Reiter's syndrome

The first written evidence for an infectious agent triggering aseptic arthritis is dated in 1916 when Fiessinger and Leroy described four patients with dysentery who presented with oculo-urethro-synovial syndrome. Reiter has described a similar condition in the same year and suspected treponema as the triggering agent of the arthritis. The disorder has been subsequently referred to as Reiter's syndrome.

Reiter's syndrome, also referred to as reactive arthritis, is defined as aseptic arthritis triggered by an infectious agent located outside the joint.

Epidemiology

Reiter's syndrome is a rare disorder. The incidence of Reiter's syndrome varies based on several factors including geographic location, presence of outbreaks of epidemics of gastroenteritides, and population sample. A study from Minnesota reports on as few as 16 cases of Reiter's syndrome documented over a thirty year period (1950-1980). On the other hand, 27 cases are reported over a three-year period (1980-1983) in the Greek army. Nine years later only four new cases of Reiter's syndrome are reported in a similar population of the Greek army. The data from Canada confirm this decreasing trend in the incidence of Reiter's syndrome. The authors report

on 12 cases per million in the mid 1980s as opposed to 3 cases per million in the mid 1990s. It is hypothesized that the decreasing trend in the incidence of Reiter's syndrome is a result of precautions related to a risk of HIV infection over that past two decades.

Pathogenesis

Reactive arthritis is characterized by an acute, sterile synovitis associated with localized infection elsewhere in the body. Bacterial trigger infections in the gut or genital tract precede the development of reactive arthritis in some patients.

Attempted isolation of microorganisms from joints typically fails. Although intracytoplasmic inclusions in the synovial fluid and synovium consistent with *C. trachomatis* were observed on light and electron microscopy, attempts to culture *C. trachomatis* failed. Some studies demonstrated the presence of *Campylobacter trachomatis*, *Yersinia pseudotuberculosis*, *Yersinia enterocolitica*, *Salmonella enteritidis*, *Salmonella typhimurium*, and *Shigella flexneri* antigens in joint specimens of the patients with Reiter's syndrome. However, the pathogenic significance of intra-articular bacterial antigens remains unclear.

Systemic manifestations

Systemic symptoms of Reiter's syndrome are typically preceded (one month or less) by acute nonspecific urethritis or acute diarrhea. Dysenteric episodes may follow after the acute diarrhea. The severity and duration of dysenteric episodes typically correlate with the severity and duration of arthritis. However, isolation of a triggering agent from the stool is rare except for salmonella. Nonspecific urethritis is typically painless and presents with non-purulent urethral discharge. Occasionally it can be associated with prostatitis or cervicitis. Reactive arthritis can present as one or more of the following four syndromes: peripheral arthritis syndrome, enthesopathic syndrome, pelvic and axial syndrome, and extramusculoskeletal syndrome.

The peripheral arthritis syndrome typically involving two to four joints (oligoarthritis) such as wrists, elbows, knees and ankles has a diagnostic sensitivity of 44.3% and a specificity of 95%. Diffuse swelling of an entire finger or toe (sausage digit) has a sensitivity of 27% and specificity of 99%. The onset of reactive arthritis involving more than four joints (polyarthritis) may be associated with fever and weight loss.

The enthesopathic syndrome affecting tendon insertions to bone is present in approximately 42% of patients. The heel is affected most frequently. The diagnostic specificity of the heel pain is 92%.

The pelvic and axial syndrome is common in patients with Reiter's syndrome and is diagnosed if inflammatory dorsal or lower back arthritis is present.

The extramusculoskeletal syndrome can involve skin, mucous membranes, gastrointestinal tract, urogenital symptoms, and/or eyes.

Balanitis circinata is an erythematous lesion of the glans penis. Similar lesions can be found on the oral mucosa. Importantly, the mucocutaneous lesions associated with Reiter's syndrome are, unlike in Behcet's disease, painless. Keratoderma blenorrhagica represents palmar or solar lesions of pustular psoriasis. More typical psoriatic lesions with hyperkeratosis and parakeratosis on the skin or nails can also be present.

Ocular manifestations

The original Reiter's report in 1916 described a patient with non-purulent conjunctivitis. Since then conjunctivitis is considered the classical part of Reiter's syndrome, although ocular manifestations can be multiple. Unfortunately, cohort studies focusing on ocular manifestations of Reiter's syndrome are missing in the literature because of the infrequency of the disorder. Therefore, anecdotal reports on cases diagnosed with Reiter's syndrome remain the only written

source of information on the ocular manifestations of this disorder. The ocular involvement typically starts within one month after the acute episode of non-specific urethritis or diarrhea. It can present as keratitis, episcleritis, scleritis, uveitis, pars planitis, and retinal vasculitis.

Whether or not there is a difference in the spectrum of ocular manifestations, severity and prognosis between patients with HLA-B27 associated ocular inflammations and those with Reiter's syndrome remains unclear.

The ocular involvement typically starts within one month or less after the acute episode of non-specific urethritis or diarrhea. It can present as keratitis, episcleritis, scleritis, uveitis, pars planitis, and retinal vasculitis.

Laboratory investigation

There are no specific laboratory tests for Reiter's syndrome. However, sedimentation rate and C-reactive protein in patients with clinical manifestations of Reiter's syndrome are usually elevated. The presence of the HLA-B27 gene is present in 50 to 80% of patients.

Therapy

Physical therapy of patients with Reiter's syndrome plays an important role in the management of arthritis. Pain in the lower back and enthesopathic pain are sensitive to non-steroidal anti-inflammatory drugs (NSAIDs). The relief usually comes within 24 to 48 hours after initiation of the therapy with NSAIDs. A recurrence of pain in the lower back within 24 hours after discontinuation of NSAIDs indicates a 73% likelihood of spondyloarthropathy.

Acute episodes of ocular manifestations are typically treated with topical and periocular steroids. A violent inflammation may require a short course of systemic corticosteroids in some cases. Patients in whom the ocular inflammation persists or recurs can be treated chronically with non-steroidal anti-inflammatory drugs. Failure of the therapy with NSAIDs is an indication for systemic immunosuppressive therapy. Complications of ocular inflammation and topical corticosteroid therapy may require surgical intervention. Importantly, surgical procedures should be performed in the absence of clinical signs of active inflammation.

Prognosis

The arthritis typically subsides within three to six months after the acute episode. In some patients, relapses of arthritis and/or ocular manifestations can occur. The first relapse of arthritis begins typically three to four years after the acute episode. The arthritis is usually non-erosive, but joint erosions are reported in some cases. Patients with Reiter's syndrome who carry HLA-B27 gene are of a higher risk for developing sacroiliitis and chronic uveitis when compared to those who are HLA-B27 negative.

Data on the prognosis of ocular involvement in Reiter's syndrome are missing. However, scattered reports in the literature, and our experience, suggest that ocular manifestations can persist for several weeks to months, and that recurrences of ocular inflammation can occur over many years.

Reiter's Syndrome

Erik Letko, M.D.

1) Reiter's syndrome, also referred to as reactive arthritis is defined as:

- a) Aseptic arthritis triggered by an infectious agent located inside the joint
- b) Aseptic arthritis triggered by an infectious agent located outside the joint

c) Aseptic arthritis following joint infection

d) Aseptic arthritis associated with ocular inflammation

2) According to some studies, the incidence of Reiter's syndrome in the past two decades is:

a) Unchanged

b) Increasing

c) Decreasing

d) Unknown

3) All of the following bacterial agents are associated with Reiter's syndrome except:

a) Neisseria gonorrhoea

b) Salmonella enteritidis

c) Yersinia enterocolitica

d) Shigella flexneri

4) Reiter's syndrome is typically preceded by acute:

a) Otitis

b) Arthritis

c) Uveitis

d) Diarrhea

5) Diffuse swelling of an entire finger or toe (dactylitis) in Reiter's syndrome has a diagnostic specificity of:

a) 27%

b) 95%

c) 99%

d) 92%

6) The diagnostic specificity of heel pain (heel enthesopathy) in Reiter's syndrome is:

a) 27%

b) 95%

c) 99%

d) 92%

7) Extramusculoskeletal signs of Reiter's syndrome can typically present as following except:

a) Oral erythematous lesions

b) Painful genital ulcers

c) Keratoderma blenorrhagica

d) Palmar or solar psoriasis

8) Ocular signs of Reiter's syndrome can present as following except:

a) Endophthalmitis

b) Keratitis

c) Scleritis

d) Retinal vasculitis

9) The HLA-B27 gene in Reiter's syndrome is present in:

a) 10-30% of patients

b) 50-60% of patients

c) 50-90% of patients

d) 50-80% of patients

10) Patients with Reiter's syndrome who carry HLA-B27 gene are in comparison to those who are HLA-B27 negative:

a) Of no risk for developing sacroiliitis and chronic uveitis.

b) Of a lower risk for developing sacroiliitis and chronic uveitis.

c) Of a higher risk for developing sacroiliitis and chronic uveitis.

d) Of the same risk for developing sacroiliitis and chronic uveitis.

Correct answers: 1b, 2c, 3a, 4d, 5c, 6d, 7b, 8a, 9d, 10c